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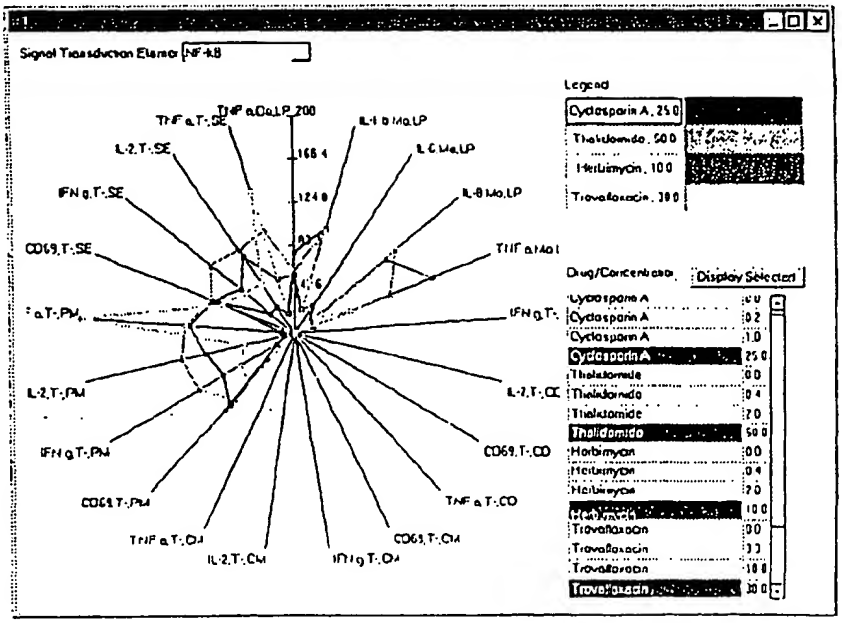
(54) Title: APPARATUS AND METHODS FOR DRUG ANALYSIS AND DEVELOPMENT



(57) Abstract: Apparatus and methods are disclosed for analyzing whole blood leukocyte response data. In a first stage, leukocyte response data are included in a database. In a second stage, various analysis techniques are provided to analyze data in the database.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

APPARATUS AND METHODS FOR DRUG ANALYSIS AND DEVELOPMENT

Field Of The Invention

The present invention relates to apparatus and methods for drug analysis and development. In particular, the present invention provides methods for providing a database that contains data describing effects of agents on leukocyte activation, and provides methods and apparatus for extracting information from the database for drug analysis and development.

Background Of The Invention

Many pharmacological agents are known to affect the immune system, and in particular, are known to affect leukocyte activation. Researchers have developed immune function assays that use flow cytometry to quantitatively measure the effect of drugs on particular leukocytes.

For example, commonly owned and copending U.S. application Ser. No. 09/158,406 to Willmann et al. (Willmann), the disclosure of which is incorporated by reference herein in its entirety, describes flow cytometry methods for measuring dendritic cell activation in whole blood. In the presence of an activator such as lipopolysaccharide (LPS), dendritic

cells increase expression of cell surface activation markers such as CD80 and CD83, and of cytokines such as TNFα. When activated in the presence of secretion inhibitors, dendritic cells retain cytokines. Thus, dendritic cell activation may be measured by monitoring the expression by dendritic cells of cell surface activation markers and intracellular cytokines.

Willmann describes methods for performing such measurements by combining a sample of whole blood with LPS in the presence of brefeldin A, and then surface-staining the cells in the sample with dendritic cell-distinguishing, fluorophore-conjugated antibodies. After removing red blood cells from the sample, the sample is further stained using antibodies labeled with flow cytometrically distinguishable fluorophores that bind specifically to cell surface activation markers and intracellular cytokines. Finally, the cells are analyzed by flow cytometry to determine the quantity of cell surface activation markers and intracellular cytokines present in the sample. Willmann also describes advantages of using such methods to monitor the effect of drugs on dendritic cell activation.

In addition, commonly assigned and copending U.S. application Ser. No. 08/803,702 to Maino et al. (Maino), the disclosure of which is incorporated herein by reference in its entirety, describes flow cytometry methods for measuring T-cell activation in whole blood. Maino teaches that such flow cytometry methods may be used to monitor the effect of a drug on T-cell activation by performing flow cytometry on blood samples with and without a drug, and then comparing the results of the two measurements. Other similar flow cytometry assays have been developed for measuring the activation of B-cells, monocytes, platelets and

basophils from samples of whole blood, and these assays may be used to monitor the effect of drugs on these leukocytes.

Indeed, the previously described whole blood flow cytometry assays may be used to provide "leukocyte response data," i.e., data that describes the effect of a particular concentration of a particular drug on the activation of a particular leukocyte cell type for a particular donor. For example, leukocyte response data may include a donor identification (e.g., name or identifying number), the drug name (e.g., cyclosporin A), the drug concentration (e.g., 25 μM), the particular leukocyte cell type that is tested (e.g., monocytes), the activator that is mixed with the whole blood (e.g., LPS), the activation marker that is monitored (e.g., TNFα), the relative change in activation in the population as a whole (e.g., 170% -- i.e., a 70% enhancement of TNFα expression compared to whole blood that has not been combined with cyclosporin A), or a change that is nonuniform among the cells of the tested population, revealing a previously unresolved drug-responsive or drug-resistant subpopulation of leukocytes.

By performing many tests on many different samples, a large quantity of leukocyte response data may be generated. Such leukocyte response data, however, have not previously been combined to quantitatively describe the immune function response when whole blood is exposed to drugs. Moreover, such data has not been combined in a manner that facilitates the analysis of the immune system when whole blood is exposed to drugs.

It therefore would be desirable to provide methods and structures for combining and storing

leukocyte response data obtained from whole blood flow cytometry assays.

It also would be desirable to provide methods and apparatus for extracting information from the stored leukocyte response data to provide multiparametric immune function analysis of whole blood that has been exposed to drugs.

Summary Of The Invention

It is an object of this invention to provide methods and structures for combining and storing leukocyte response data obtained from previously known flow cytometry assays.

It also is an object of this invention to provide methods and apparatus for extracting information from the stored leukocyte response data to provide multiparametric immune function analysis of whole blood that has been exposed to drugs.

These and other objects of the present invention are achieved by providing systems that store leukocyte response data in a leukocyte response database and provide software for analyzing data in the database. A server computer may store leukocyte response data in a leukocyte response database, and users may interact with the server computer over an Intranet or the Internet. A user may communicate with the system using a standard web browser, and may extract and display data from the database in the web browser.

The leukocyte response database may contain data provided by one or more researchers working within a single entity (e.g., a single corporation, research laboratory, or university), or may be collaboratively provided by many researchers working at many different

locations throughout the world (e.g., many corporations, laboratories and universities). By combining validated data from multiple sources, data in the leukocyte response database may be continually updated and expanded to reflect the latest research.

Brief Description Of The Drawings

These and other objects and advantages of the present invention will be apparent upon consideration of the following detailed description, taken in conjunction with the accompanying drawings, in which like reference characters refer to like parts throughout, and in which:

FIG. 1 shows a database construction stage of the present invention;

FIG. 2 shows an illustrative database record in accordance with this invention;

FIG. 3 shows an illustrative data extraction process in accordance with this invention;

FIGS. 4A and 4B show illustrative displays of results of a data extraction process in accordance with this invention;

FIG. 5 shows another illustrative data extraction process in accordance with this invention;

FIG. 6 shows another illustrative database record in accordance with this invention;

FIG. 7 shows another illustrative data extraction process in accordance with this invention;

FIG. 8 shows another illustrative display of results of a data extraction process in accordance with this invention;

FIG. 9 shows another illustrative data extraction process in accordance with this invention;

FIG. 10 shows another illustrative data extraction process in accordance with this invention;

FIG. 11 shows another illustrative display of results of a data extraction process in accordance with this invention; and

FIG. 12 shows an illustrative computer network on which the database and methods of the present invention may be implemented.

Detailed Description Of The Invention

This invention provides a system for storing leukocyte response data in a database and for extracting data from the database. The system comprises a database construction stage, in which leukocyte response data are collected and stored in a leukocyte response database, and a data analysis stage that may be used to analyze data in the database.

As used herein, a database is a compilation of data stored on a computer system, such as in computer memory. A database may contain records, organized into one or more fields that each identify a specific data type (e.g., leukocyte cell type, leukocyte activators, etc.). Thus, a record comprises data populating each of the fields associated with the record, although some fields may have null values.

Referring to FIG. 1, an illustrative database construction stage of a system of this invention is described. In this stage, leukocyte response data are collected to create a leukocyte response database. Leukocyte response data 10 may be generated by researchers at a single institution, such as a single pharmaceutical company or university, or may be generated by researchers from many different institutions. Because data 10 may be provided by a

wide variety of sources, it may be desirable to screen the data before including it in leukocyte response database 16. Thus, data 10 may be provided to a scientific review board, which reviews data at step 12 (e.g., for scientific validity) to determine whether the data should be included in leukocyte response database 16.

At step 14, data that has been reviewed is checked to see if it meets predetermined inclusion criteria (e.g., covers leukocyte response data of interest to a particular user community) and should be included in database 16. If the data meets the inclusion criteria, the data are stored in database 16. If the data do not meet the inclusion criteria, the data are not included in database 16, and the review of the data may be archived at step 18.

Leukocyte response data are stored in database 16 in leukocyte response records. Referring to FIG. 2, an illustrative leukocyte response record is described. Leukocyte response record 20 contains six data fields: 22, 24, 26, 28, 30 and 32. Field 22 specifies the drug name (e.g., cyclosporin A), and field 24 describes the drug concentration (e.g., 25 μM). Field 26 specifies leukocyte cell type (e.g., B-cells, T-cells, monocytes, etc.), field 28 describes the cell activators used to activate that cell type (e.g., LPS, CD40 and IL-4, SEB, CD28 and CD49d, etc.), and field 30 describes the activation markers examined (e.g., Il-1β, CD25, CD69, etc.). Field 32 describes the response of the leukocyte to the drug (e.g., expression of IL-1β in a sample containing 25 μM cyclosporin A was 115% of the expression in a sample containing no drug). Although six fields are shown in FIG. 2, more or fewer fields may be included

in a leukocyte response record. Each record may have a fixed or variable number of fields, some of which may have null values. As described in more detail below, for example, additional fields may be included in each record.

Database 16 preferably will be populated with many records for many different leukocyte cell types, tested with many different concentrations of many different drugs. In addition, database 16 preferably will be populated with records having leukocyte response data from many individual blood donors. Once sufficient leukocyte response data are available in leukocyte response database 16, systems of this invention may be used to analyze data in database 16.

For example, it may be desirable to extract all leukocyte response data for a particular concentration of a particular drug. Referring to FIG. 3, the steps required to provide such a leukocyte response profile are described. At step 34, the system receives information from a user who may interact directly with the computer, or may interact with the computer via the Internet. At step 34, the system requests the drug name and concentration. At step 36, the system scans leukocyte response data from database 16 to determine if any data match the request. At step 38, the system determines if any data match the user's request. If no data match, the system at step 40 reports to the user that no data match the request. If database 16 contains matching data, the system at step 42 displays the leukocyte response profile for the user.

An illustrative display of a leukocyte response profile is shown in FIG. 4A. Display 44 shows the response of a subpopulation of leukocytes 50 (e.g.,

B-cells, T-cells, monocytes, platelets, dendritic cells and basophils) to concentration 48 (e.g., 25 μM) of drug 46 (e.g., cyclosporin A). Display region 52 shows activators used for each cell type, and display region 50 shows the response of cell activation markers for each cell type. Display 44 may be a multicolor display, with different colors indicating response suppression or enhancement, as indicated by legend 56. As shown in FIG. 4A, for 25 μM of cyclosporin A, the response of TNFα in monocytes is enhanced to approximately 155-180% compared to a baseline response (i.e., in the absence of any drug).

Systems of this invention may perform other analyses of data in database 16. During drug development, it may be desirable to visually compare the leukocyte responses of two different drugs. The system may receive information from the user as to which drugs and which cell types to display, and then may display the leukocyte response profiles for the drugs. FIG. 4B shows leukocyte response data for two different drugs: herbimycin (upper trace) and cyclosporin A (lower trace).

In addition, during drug analysis and development, it may be desirable to match an unknown drug to known drugs to predict the pharmacologic effect of the unknown drug. Systems in accordance with this invention may be used to match the leukocyte response of the unknown drug (e.g., compound X) with the leukocyte responses of drugs in database 16.

For example, as shown in FIG. 5, the system at step 60 receives leukocyte response data for the unknown drug from a user. At step 62, the system searches database 16 to match leukocyte response profiles for the unknown drug with leukocyte response

profiles for known drugs in the database. The system may use any of a number of previously known estimation techniques, such as minimum least-squares error techniques, or other suitable techniques. At step 64, the system displays the results to the user.

The system may display a result indicating that compound "X" has a leukocyte response profile that most closely matches the leukocyte response profile of penicillin. From this result, the user may conclude that compound "X" may have other pharmacologic properties that are similar to those of penicillin. Thus, if it is known that a given concentration of penicillin in whole blood is toxic, the user may conclude from the analysis that a similar concentration of compound "X" in whole blood also may be toxic.

Systems of this invention also may be used for drug characterization and stratification of the patient population. The leukocyte response profile for a particular concentration of a particular drug by patients who share a particular characteristic or genetic profile may be distinct from the response of patients who lack the characteristic or genetic profile. Thus, for example, patients with high blood pressure may have a leukocyte response profile for herbimycin that distinctively differs from the response profile of patients with normal blood pressure. Leukocyte response records in leukocyte response database 16 may include such additional characteristics, and the system of the present invention may be used to identify these common characteristics.

As shown in FIG. 6, a leukocyte response record 66 of this invention may include the same fields as record 20 shown in FIG. 2, but also may include

three additional fields 68, 70 and 72 that may be used to include additional characteristics about individual patients. For example, fields 68, 70 and 72 may be used to indicate that the patient is male, overweight, and hypoglycemic, respectively.

Using the information in the additional leukocyte response record fields, systems in accordance with this invention may be used for drug characterization and stratification of patient population. Referring to FIG. 7, the system at step 74 receives individual screening factors from the user. For example, the user may request that the system sort the data in database 16 based on whether the patient is hypoglycemic. At step 76, the system sorts the data, averages the leukocyte response data from all patients who are hypoglycemic, and separately averages the leukocyte response data from all patients who are non-hypoglycemic. At step 78, the system displays the results to the user. FIG. 8 illustrates an exemplary display of such a search, which indicates that in hypoglycemic patients, a concentration of 25 μM of drug "Y" boosted the expression of IL-2 in T-cells.

Systems in accordance with this invention also may be used to integrate leukocyte response data with data contained in other scientific and in-house databases to provide additional information useful for drug development. As shown in FIG. 9, at step 80, the system displays the leukocyte response profile for drug "Z," which has a certain desirable response. For example, the leukocyte response profile may indicate that 10 μM of drug "Z" boosts T-cell activation. Nevertheless, the researcher may be uncertain about some other characteristic of drug "Z," such as the drug's bioavailability. At step 82, the system may

provide links to other databases that may provide such information, such as a structure activity relationship (SAR) database that contains additional information about drug "Z" or its chemical constituents.

In the SAR database, the researcher may discover that the bioavailability of drug "Z" is unacceptably low, but may recognize through links and other query tools that by modifying the structure of drug "Z," the bioavailability may be increased. The researcher may then synthesize the modified drug (e.g., drug "Z'"), and determine that the bioavailability of drug "Z'" in fact is higher than that of drug "Z." The researcher preferably also would determine whether drug "Z'" shares the same desirable leukocyte response profile as drug "Z." Thus, at step 84, the system receives leukocyte response data for drug "Z'" from the user, and at step 86, the system compares the leukocyte response profiles of drug "Z'" with drug "Z." At step 88, the system displays the result to the user. If the leukocyte response profile for drug "Z'" is unacceptable, the user may wish to evaluate other synthesized drugs (e.g., drug "Z''"). Accordingly, at step 90, the system may ask whether the user wants to evaluate the leukocyte response profile of other drugs. If YES, the system repeats steps 84-90. If NO, the system may provide other options at step 92.

Systems in accordance with this invention also may be used to assist genetic research by integrating leukocyte response data with data contained in genetic databases.

For example, if records in database 16 include a field containing donor identification information, links to genetic databases similarly indexed may permit the identification of correlations

between lymphocyte response profiles and expression data for other types of genes, or may permit the identification of correlations of lymphocyte response profiles with SNPs, presence or absence of microsatellite repeats, identifiable RFLPs, or other detectable genetic sequence variation.

The system of the present invention also may be used to learn how drugs affect the immune response. For example, a researcher may know that particular concentrations of four different drugs each suppress the leukocyte response, and may hypothesize that the drugs' activity affects a particular signal transduction intermediate common to one or more activation markers for one or more leukocyte cell types. If the leukocyte response record for database 16 includes an additional field for signal transduction intermediates (e.g., NF-κB), the system of the present invention may provide information that is used to confirm or disprove the hypothesis.

Referring to FIG. 10, the system at step 94 first receives information from the user (e.g., sort data for four drugs based on signal transduction element NF-κB). At step 96, the system sorts the data from database 16 based on the user-identified signal transduction element. At step 98, the system displays the results to the user. FIG. 11 illustrates an exemplary display, which shows that each of the four drugs affects NF-κB-dependent signal transduction pathways differently, and thus confirms the hypothesis.

FIG. 12 depicts an illustrative computer system and network on which systems of the present invention may be implemented. Internet server 100 comprises a computer connected to the Internet via a high-speed connection, and is also connected to

LAN 102. Internet server 100 preferably runs a standard HTTP server application, such as Apache, which is available for free from the Apache organization at "http://www.apache.org". Internet server 100 accepts HTTP connections from computers on the Internet, and sends web pages across the Internet to client computers, such as client computer 104.

Internet server 100 also runs a variety of scripts (such as Java "servlets" or CGI scripts) to interact with users across the Internet, to dynamically build web pages, and to access data stored on database server 106. Most of the routines for interacting with a user, and for analyzing data in database 16 are stored and executed on Internet server 100.

Database server 106 comprises a computer system connected to LAN 102 that provides access to database 16, which is stored on RAID array 110. Database server 106 executes database software that permits other computers to access database 16 over LAN 102. LAN 102 also may be connected to additional computers 108, that may be used, for example, to enter leukocyte response data into database 16. Most of the functions that are performed using computers 108 connected to LAN 102 also may be performed over the Internet.

Researchers may use a personal computer connected to the Internet, such as client computer 104, to access the system of the present invention. Client computer 104 executes standard Internet browser software, such as Netscape Navigator, by Netscape Communications Corporation, of Mountain View, California. Client computer 104 uses the browser software to interact with Internet server 100 across the Internet, and to display web pages provided by

Internet server 100 to the user. Input forms generated by the system of the present invention, as well as the displays generated by the system are displayed to the user by the browser software running on client computer 104.

It should be understood that the network configuration discussed with reference to FIG. 12 is for purposes of illustration only. It would be possible, for example, to combine database server 106 with Internet server 100. Additionally, database 16 may be stored on a normal hard drive or other magnetic media, an optical disk, or in a distributed fashion on computers 108 on LAN 102, rather than on RAID array 110. The exact configuration of LAN 102, or the specific software and protocols used on the computers connected to LAN 102 all may be changed without departing from the present invention.

Although preferred illustrative embodiments of the present invention are described above, it will be evident to one skilled in the art that various changes and modifications may be made without departing from the invention. Additionally, minor variations of the structure of the database, or of the algorithms used to generate the profiles may be made without significantly affecting the overall structure or operation of the system. It is intended in the appended claims to cover all such changes and modifications that fall within the true spirit and scope of the invention.

We claim:

1. A method for building a leukocyte response database, the method comprising:

reviewing leukocyte response data based on a set of scientific criteria;

selecting reviewed leukocyte response data for inclusion in a leukocyte response database based on a set of predetermined inclusion criteria; and

storing the selected leukocyte response data in a database.

2. A digital storage medium storing a leukocyte response database, the database comprising:

a plurality of leukocyte response records, each leukocyte response record comprising a plurality of fields containing information on results of a leukocyte response test.

3. The digital storage medium of claim 2, wherein the plurality of fields comprises:

a drug name field that contains a name of a drug used in the test;

a drug concentration field that contains a concentration of the drug;

a cell type field that contains a name of a leukocyte cell type that was studied in the test;

an activators field that contains a name of one or more activators used in the test;

an activation markers field that contains a name of one or more activation markers that were studied in the test; and

a response field that contains a value indicating the response of the cell type to the drug.

4. The digital storage medium of claim 3 wherein each record comprises information on the results of a leukocyte response of an individual mammal, and the plurality of fields further comprises at least one characteristic field that describes a characteristic of the mammal.

5. The digital storage medium of claim 2 wherein the plurality of fields further comprises a signal transduction field that contains a name of a signal transduction intermediate of the activation marker.

6. A computer system for generating a leukocyte response profile, the computer system comprising:

a leukocyte response database comprising leukocyte response data for a plurality of drugs, the data stored in a plurality of records, each record comprising a drug name, a drug concentration, a cell type, an activator, an activation marker and a response;

a data collection routine that collects information from a user for a concentration of a drug;

a searching routine that searches the database for records that include the concentration of the drug; and

an output routine that generates the leukocyte response profile from results of the search by the search routine.

7. The computer system of claim 6, wherein the output routine comprises a display routine that displays the leukocyte response profile for the user.

8. The computer system of claim 7, wherein the display routine displays the results in a multicolor display.

9. The computer system of claim 6, wherein the data collection routine, searching routine and output routine are implemented on an Internet server, and the user interacts with the routines via the Internet.

10. A computer system for generating leukocyte response profiles, the computer system comprising:

a leukocyte response database comprising leukocyte response data for a plurality of drugs, the data stored in a plurality of records, each record comprising a drug name, a drug concentration, a cell type, an activator, an activation marker and a response;

a data collection routine that collects information from a user for first and second drug names;

a searching routine that searches the database for records that include the first and second drug names; and

an output routine that generates leukocyte response profiles from results of the search by the search routine.

11. The computer system of claim 10, wherein the data collection routine, searching routine and output routine are implemented on an Internet server, and the user interacts with the routines via the Internet.

12. A computer system for drug matching, the computer system comprising:

a leukocyte response database comprising leukocyte response data for a plurality of drugs, the data stored in a plurality of records, each record comprising a drug name, a drug concentration, a cell type, an activator, an activation marker and a response;

a data collection routine that collects leukocyte response data from a user for a first drug;

a matching routine that matches the leukocyte response data for the first drug with leukocyte response data from the database; and

an output routine that reports the results of the match by the matching routine.

13. The computer system of claim 12, wherein the data collection routine, matching routine and output routine are implemented on an Internet server, and the user interacts with the routines via the Internet.

14. The computer system of claim 12, wherein the matching routine comprises a minimum least squares error analysis routine.

15. A computer system for drug screening, the computer system comprising:

a leukocyte response database comprising leukocyte response data for a plurality of drugs, the data stored in a plurality of records, each record comprising a drug name, a drug concentration, a cell type, an activator, an activation marker, a response, and a patient characterization;

a data collection routine that collects a screening factor from a user for a first drug;

a searching routine that searches the database for records that include the screening factor; and

an output routine that generates leukocyte response profiles from results of the search by the search routine.

16. The computer system of claim 15, wherein the data collection routine, searching routine and output routine are implemented on an Internet server, and the user interacts with the routines via the Internet.

17. The computer system of claim 15 further comprising:

an averaging routine that averages the leukocyte response data for records that include the screening factor, and averages the leukocyte response data for records that do not include the screening factor.

18. A computer system for drug development, the system comprising:

a leukocyte response database comprising leukocyte response data for a plurality of drugs, the data stored in a plurality of records, each record comprising a drug name, a drug concentration, a cell type, an activator, an activation marker, a response, and a patient characterization;

an output routine that outputs a leukocyte response profile for a first drug;

a link routine that provides links to a second database comprising other data about the first drug;

a data collection routine that collects leukocyte response data from a user for a second drug;

a comparison routine that compares the leukocyte response data of the first and second drugs; and

a display routine that displays the results of the comparison by the comparison routine.

19. The computer system of claim 18, wherein the output routine, link routine, data collection routine and comparison routine are implemented on an Internet server, and the user interacts with the routines via the Internet.

20. A computer system for drug analysis, the computer system comprising:

a leukocyte response database comprising leukocyte response data for a plurality of drugs, the data stored in a plurality of records, each record comprising a drug name, a drug concentration, a cell type, an activator, an activation marker, a response and a signal transduction intermediate;

a data collection routine that collects information from a user for a signal transduction element;

a searching routine that searches the database for records that include the signal transduction element; and

an output routine that generates the leukocyte response profile from results of the search by the search routine.

21. The computer system of claim 20, wherein the data collection routine, searching routine and output routine are implemented on an Internet server, and the user interacts with the routines via the Internet.

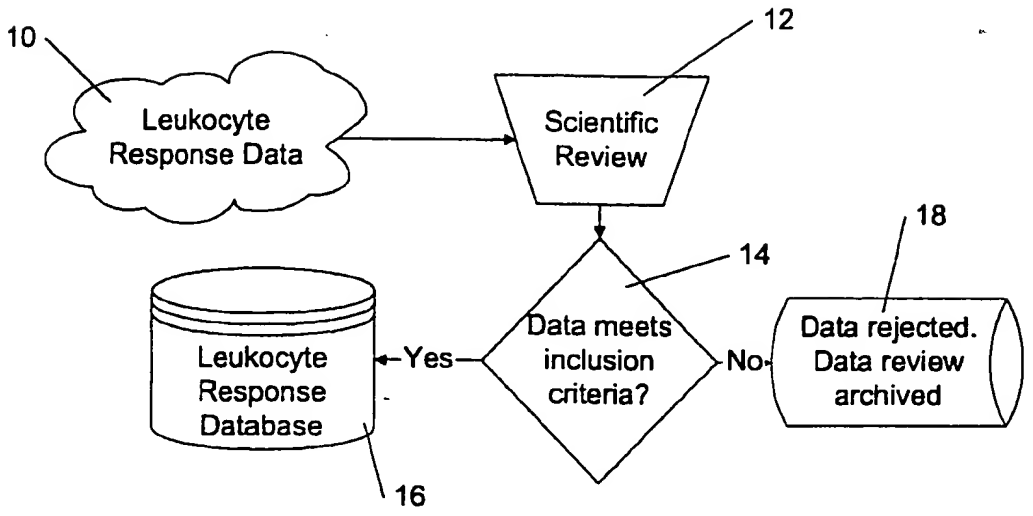
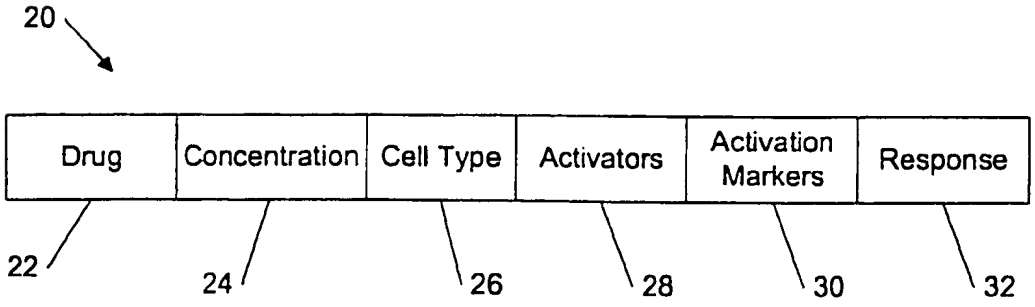

10
Leukocyte Response Data
12
Scientific Review
14
Data meets inclusion criteria?
Yes
No
18
Data rejected. Data review archived
Leukocyte Response Database
16

FIG. 1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Drug
Concentration
Cell Type
Activators
Activation Markers
Response
22
24
26
28
30
32

FIG. 2

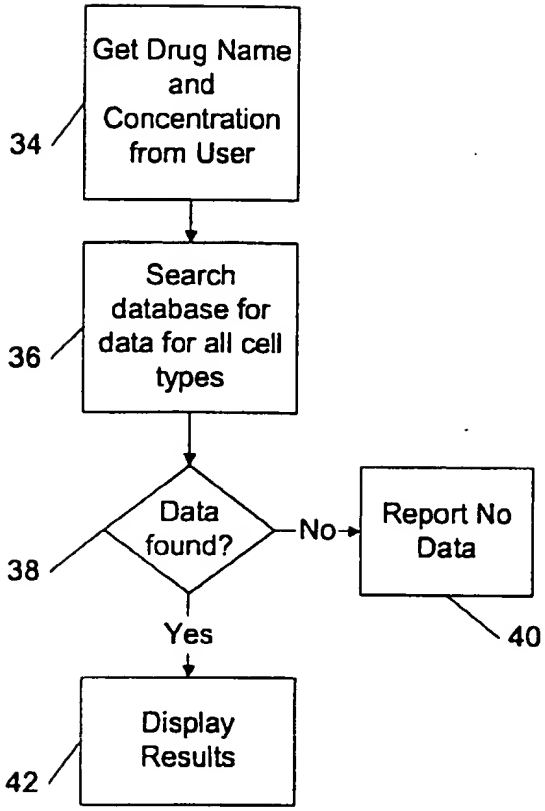
Get Drug Name and Concentration from User
34
Search database for data for all cell types
36
Data found?
38
No
Report No Data
40
Yes
Display Results
42

FIG. 3

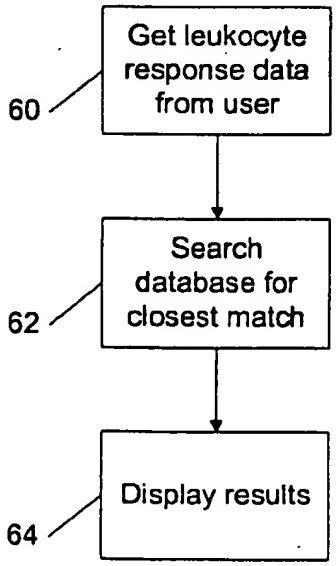
Get leukocyte response data from user
60
Search database for closest match
62
Display results
64

FIG. 5

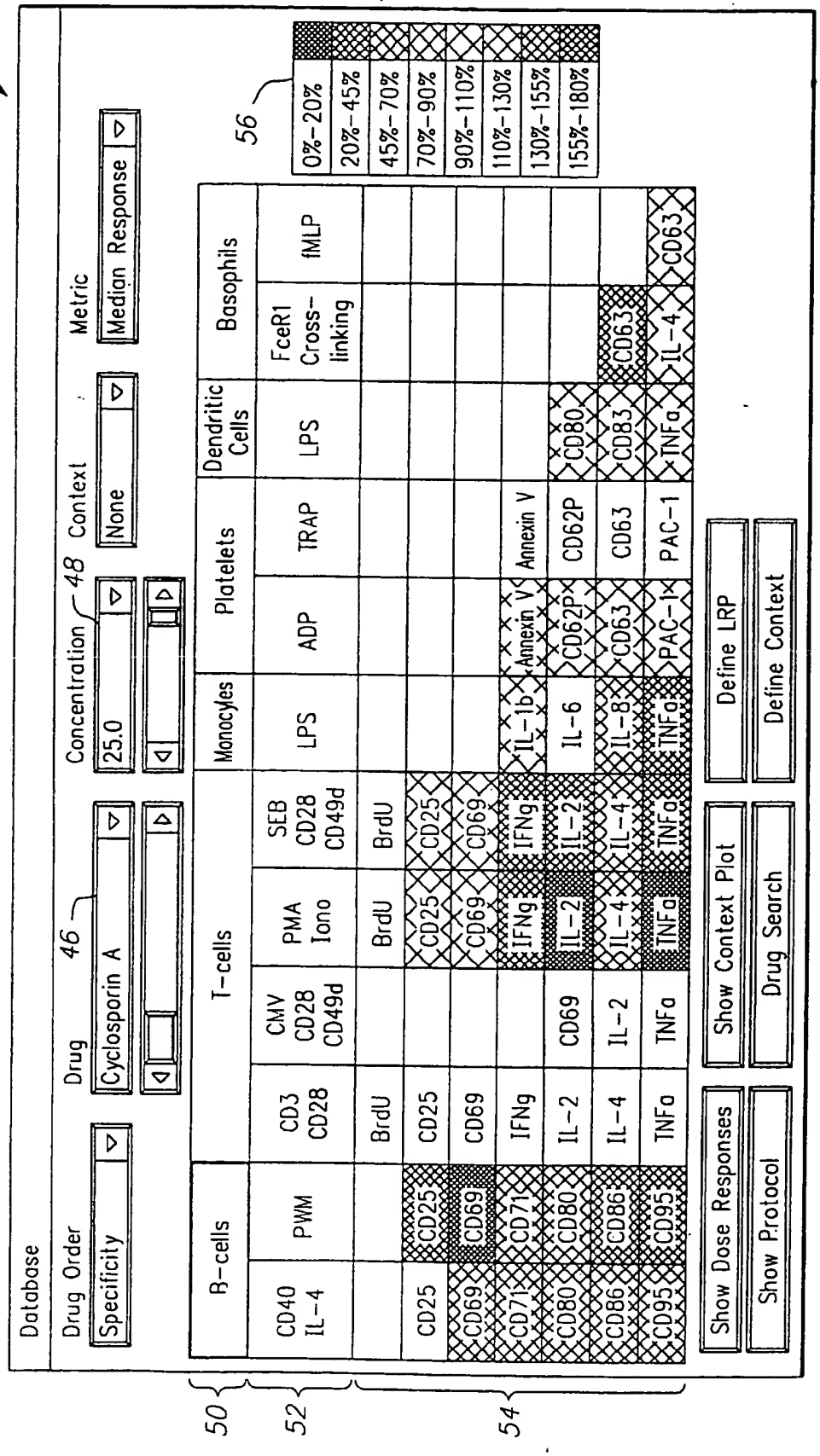
44
Database
Drug Order
Specificity
Drug
46
Cyclosporin A
Concentration
48
25.0
Context
None
Metric
Median Response
56
0%-20%
20%-45%
45%-70%
70%-90%
90%-110%
110%-130%
130%-155%
155%-180%
B-cells
CD40 IL-4
PWM
CD25
CD69
CD71
CD80
CD86
CD95
T-cells
CD3 CD28
BrdU
CD25
CD69
IFNg
IL-2
IL-4
TNFa
CMV CD28 CD49d
CD69
IL-2
TNFa
PMA Iono
BrdU
CD25
CD69
IFNg
IL-2
IL-4
TNFa
SEB CD28 CD49d
BrdU
CD25
CD69
IFNg
IL-2
IL-4
TNFa
Monocytes
LPS
IL-1b
IL-6
IL-8
TNFa
Platelets
ADP
Annexin V
CD62P
CD63
PAC-1
TRAP
Annexin V
CD62P
CD63
PAC-1
Dendritic Cells
LPS
CD80
CD83
TNFa
Basophils
FceR1 Cross-linking
CD63
IL-4
fMLP
CD63
Show Dose Responses
Show Protocol
Show Context Plot
Drug Search
Define LRP
Define Context
50
52
54

FIG. 4A

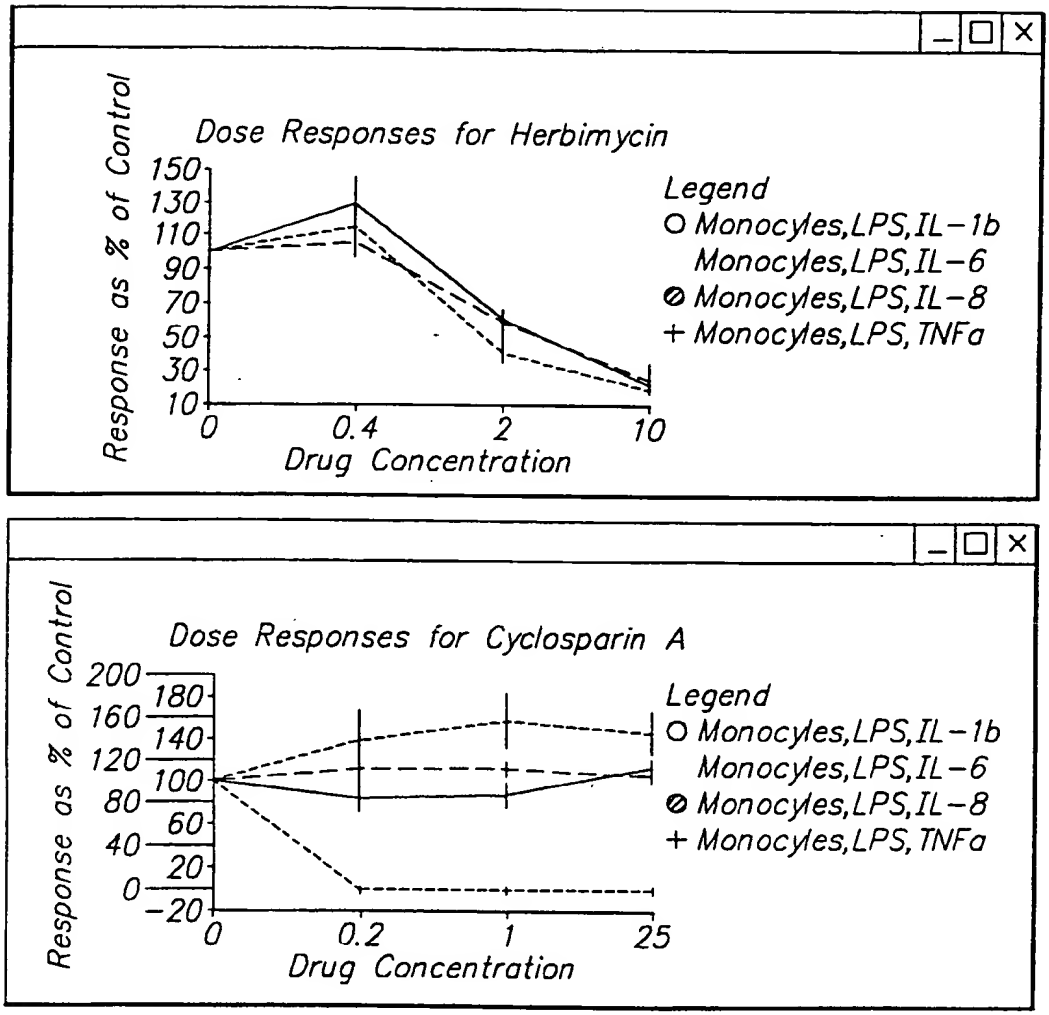
Dose Responses for Herbimycin
Response as % of Control
150
130
110
90
70
50
30
10
0
0.4
2
10
Drug Concentration
Legend
O Monocyles,LPS,IL-1b
Monocyles,LPS,IL-6
⊘ Monocyles,LPS,IL-8
+ Monocyles,LPS,TNFa
Dose Responses for Cyclosparin A
Response as % of Control
200
180
160
140
120
100
80
60
40
20
0
-20
0
0.2
1
25
Drug Concentration
Legend
O Monocyles,LPS,IL-1b
Monocyles,LPS,IL-6
⊘ Monocyles,LPS,IL-8
+ Monocyles,LPS,TNFa

FIG. 4B

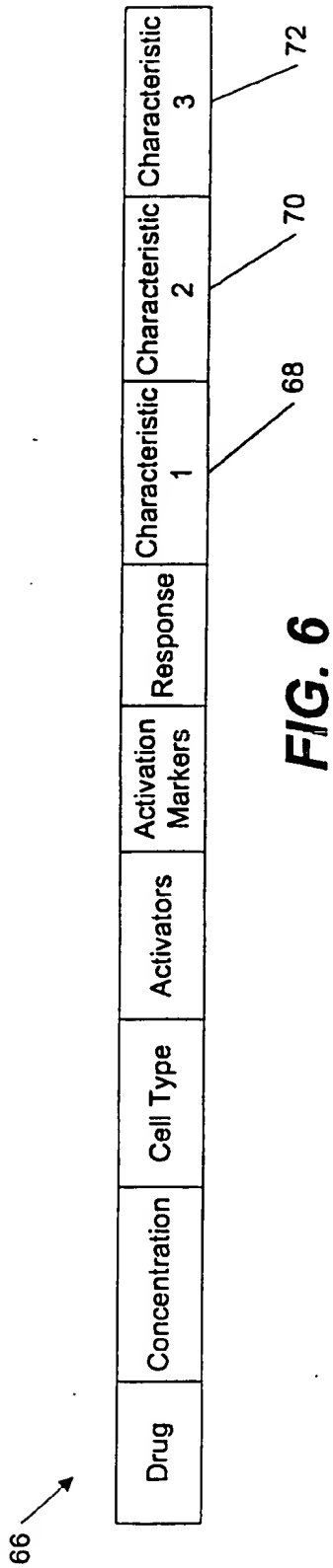
66
Drug
Concentration
Cell Type
Activators
Activation Markers
Response
Characteristic 1
Characteristic 2
Characteristic 3
68
70
72

FIG. 6

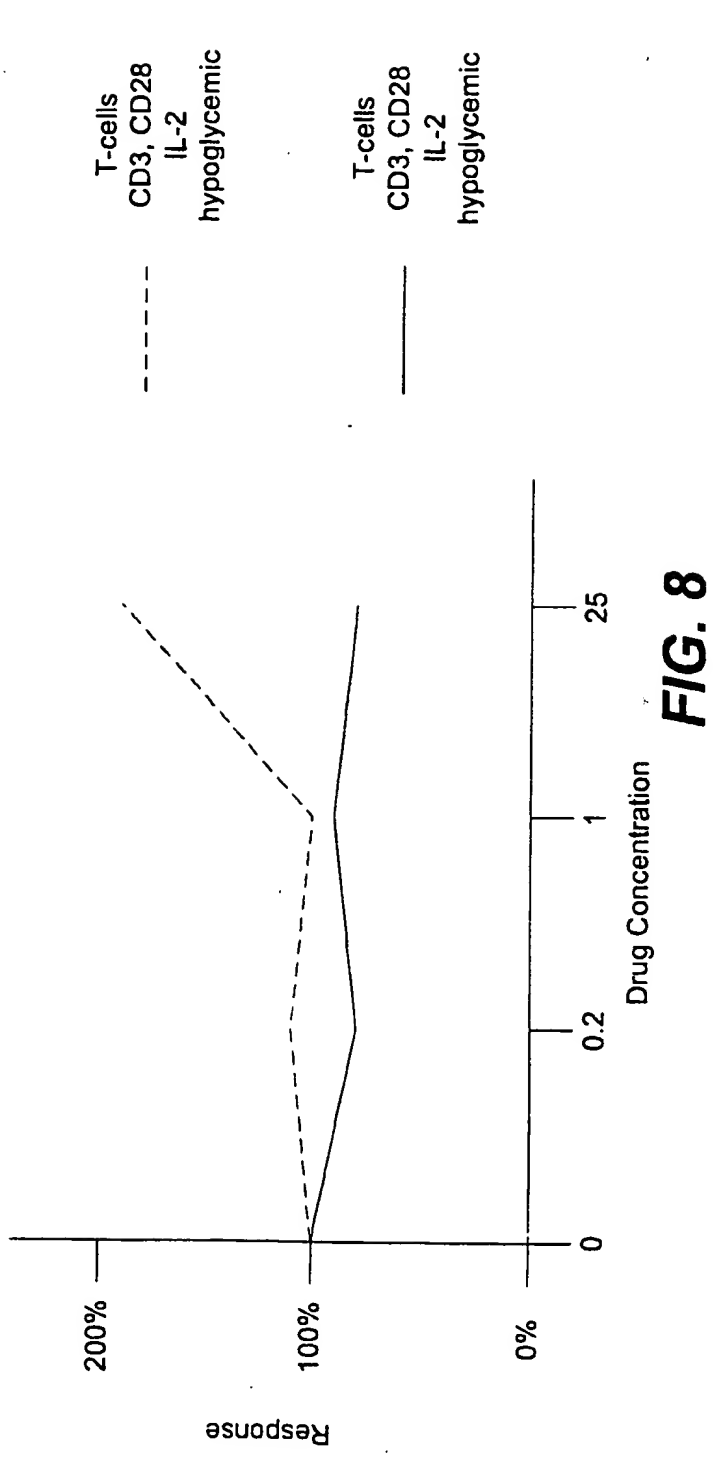
T-cells
CD3, CD28
IL-2
hypoglycemic
T-cells
CD3, CD28
IL-2
hypoglycemic
Response
200%
100%
0%
0
0.2
1
25
Drug Concentration

FIG. 8

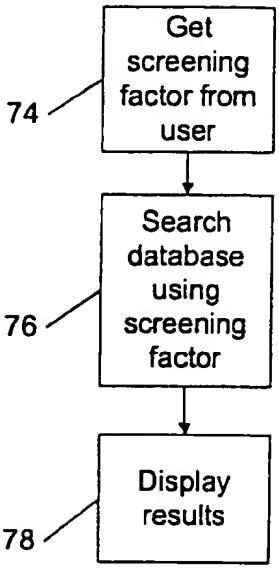

FIG. 7

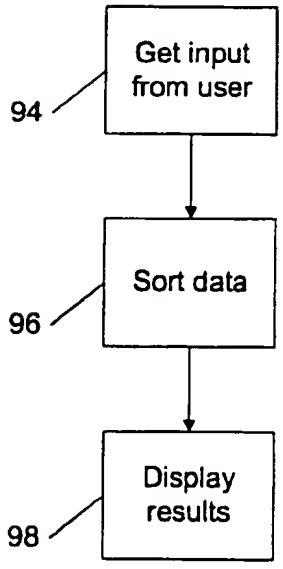

FIG. 10

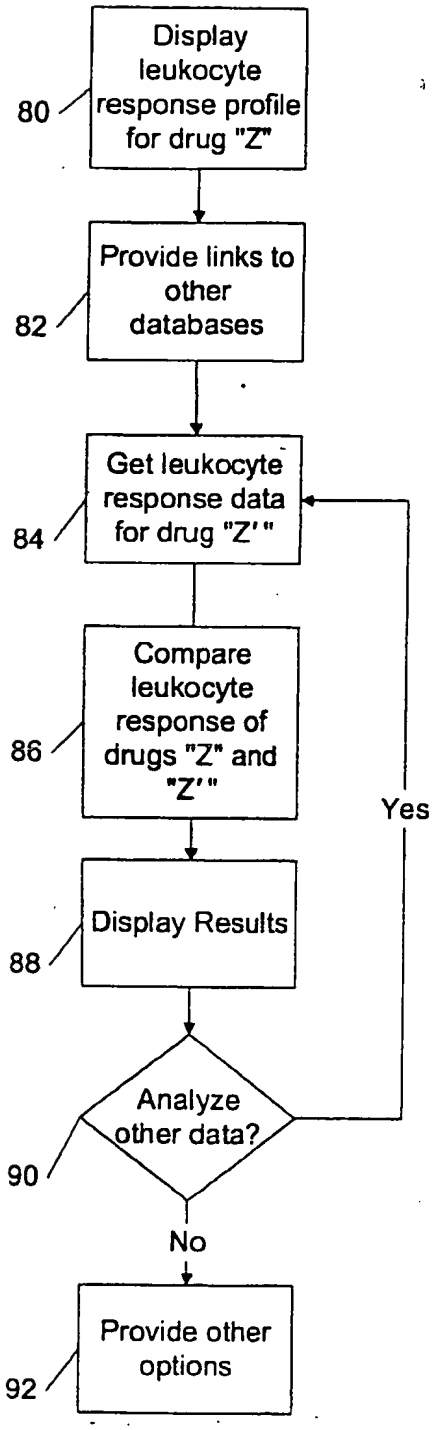

FIG. 9

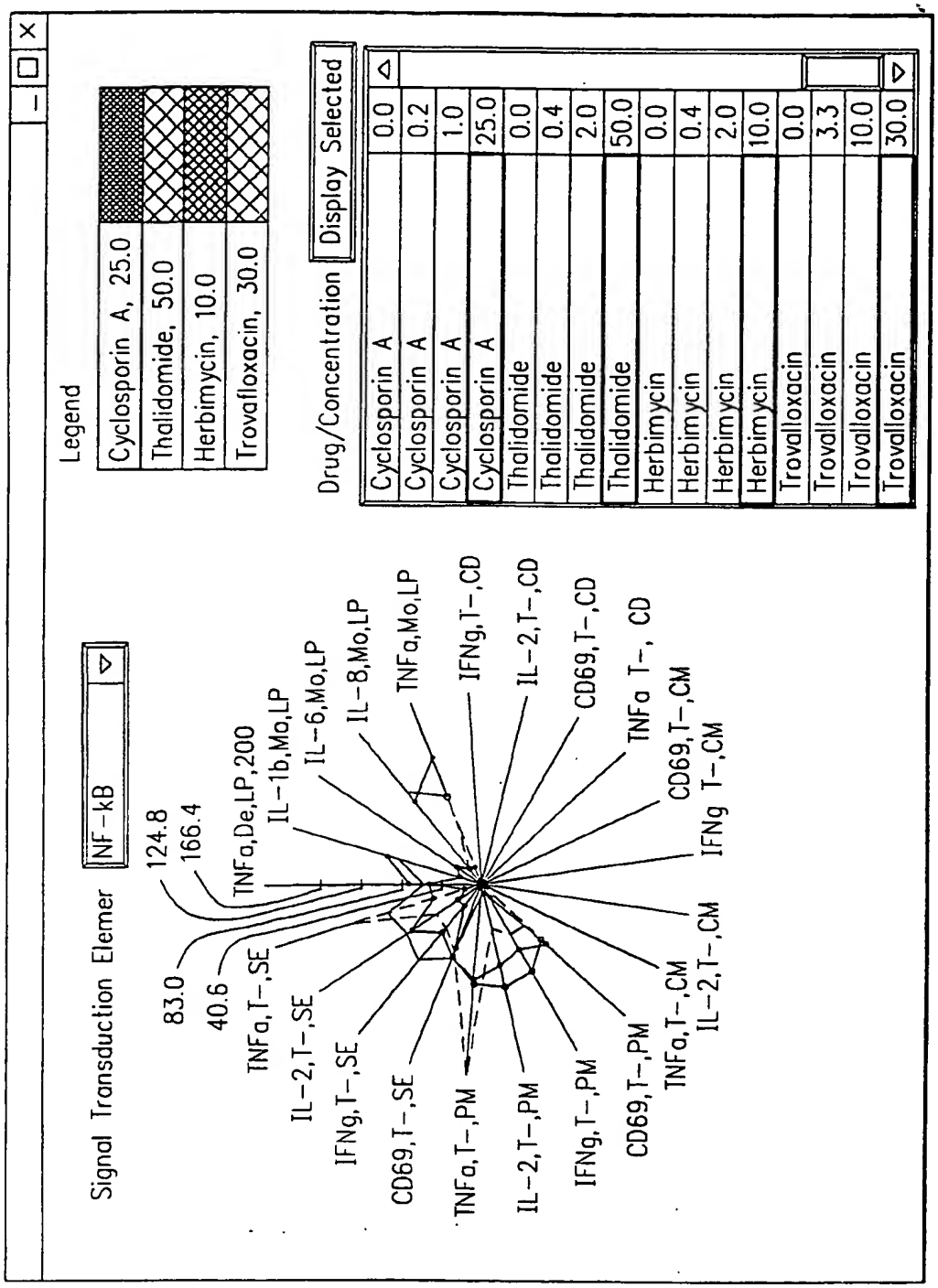
Legend
Cyclosporin A, 25.0
Thalidomide, 50.0
Herbimycin, 10.0
Trovafloxacin, 30.0
Drug/Concentration
Display Selected
Cyclosporin A 0.0
Cyclosporin A 0.2
Cyclosporin A 1.0
Cyclosporin A 25.0
Thalidomide 0.0
Thalidomide 0.4
Thalidomide 2.0
Thalidomide 50.0
Herbimycin 0.0
Herbimycin 0.4
Herbimycin 2.0
Herbimycin 10.0
Trovalloxacin 0.0
Trovalloxacin 3.3
Trovalloxacin 10.0
Trovalloxacin 30.0
Signal Transduction Elemer
NF-kB
124.8
166.4
83.0
40.6
TNFa,De,LP,200
IL-1b,Mo,LP
IL-6,Mo,LP
IL-8,Mo,LP
TNFa,Mo,LP
IFNg,T-,CD
IL-2,T-,CD
CD69,T-,CD
TNFa T-, CD
CD69,T-,CM
IFNg T-,CM
IL-2,T-,CM
TNFa,T-,CM
CD69,T-,PM
IFNg,T-,PM
IL-2,T-,PM
TNFa,T-,PM
CD69,T-,SE
IFNg,T-,SE
IL-2,T-,SE
TNFa,T-,SE

FIG. 11

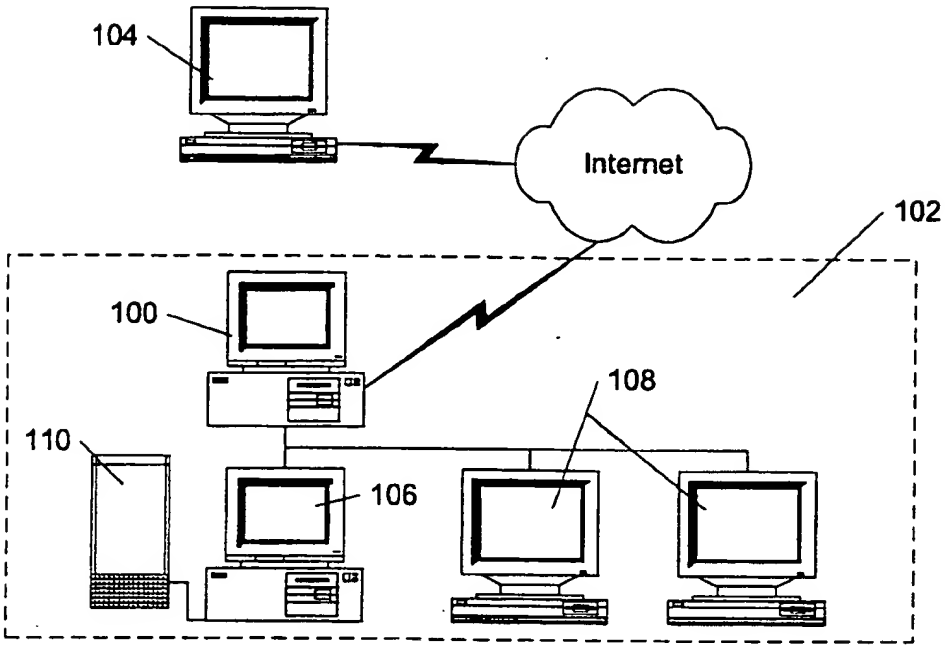

FIG. 12